Possible Approaches to the Development of Correlates of Protection for Plague Vaccines

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FDA/CBER

"Animal Rule"

New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible

Final Rule
Federal Register 67:37988-37998 May 31, 2002
21 CFR 601.90-95 (biologicals)
21 CFR 314.600-650 (drugs)

Application of the "Animal Rule"

This rule will apply when adequate and well-controlled clinical studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers and field trials are not feasible.

- **two predominant forms of plague (bubonic and pneumonic)**
- **if used as an agent of bioterrorism, the most likely form of delivery would be through aerosol dispersal causing pneumonic plague**
- **previous killed whole-cell vaccine ineffective in providing protection against aerosol challenge in animal models**

CBER

"Animal Rule" Requirements:

FDA will rely on the evidence from animal studies when:

1. **There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product.**

- ***Y. pestis* pathogenesis and associated virulence factors that lead to disruption of the innate immune response**
- **anti-phagocytic activity of the F1 capsule and the multiple functions attributed to LcrV**

"Animal Rule" Requirements:

FDA will rely on the evidence from animal studies when:

2. **The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.**

In what animal species:

- **can protection (*i.e.* survival) be measured?**
- **does the clinical disease look like that presented in humans?**
- **the elicited immune response resemble that of the human immune response?**

"Animal Rule" Requirements:

FDA will rely on the evidence from animal studies when:

3. **The animal study endpoint is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity.**

- **since *Y. pestis* is considered as a biothreat agent with aerosolization the most likely route of dispersal, animal studies should measure protection (*i.e.* survival) from an aerosol challenge**

"Animal Rule" Requirements:

FDA will rely on the evidence from animal studies when:

4. **The data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well understood to allow selection of an effective dose in humans, and it is therefore reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans.**

- **What are the protective immune responses and how are they best demonstrated?**

To Establish Correlates of Protection

Evaluate immune response in appropriate animal models

- type of immune response
- magnitude of response that is protective

Estimate the magnitude of the immune response that would protect humans

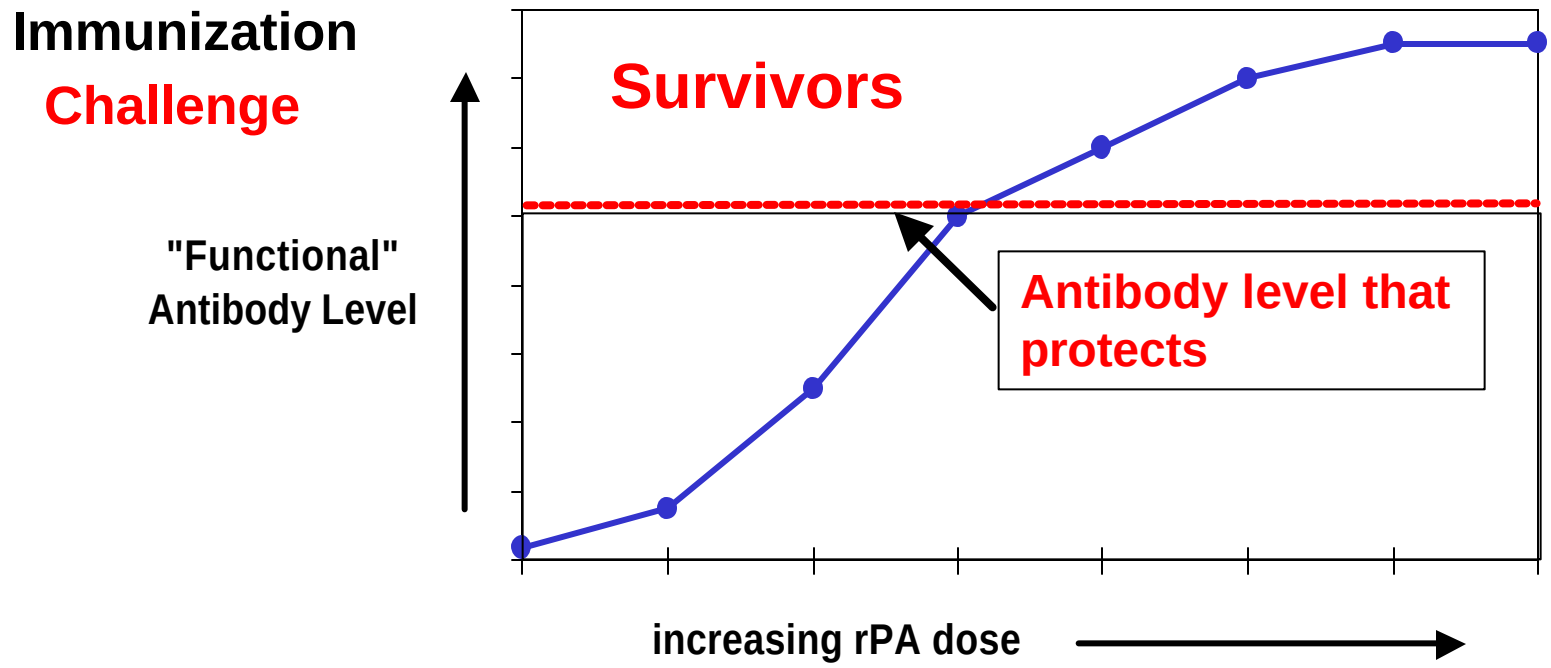
- quantity of antibody or other parameters

Evaluate immunogenicity in humans to determine the % of people that would respond in such a way that they would be protected

- data from clinical trials

Evaluation of efficacy in appropriate animal models

1. Active Immunization Studies
   - simple example – neutralizing antibodies against rPA confer protection



Evaluation of efficacy in appropriate animal models

Additional points that need to be considered for plague candidate vaccines:

1) What type of immune response is elicited?

- **Protection appears to be principally but not completely mediated by antibody**
- **What role do the CMI responses play and do these responses correlate with protection?**

Evaluation of efficacy in appropriate animal models

Additional points that need to be considered for plague candidate vaccines:

2) The immune response elicited needs to be considered for each of the two antigens

- **How should protective levels be independently assessed for both the F1 and V antigens?**

Evaluation of efficacy in appropriate animal models

Additional points that need to be considered for plague candidate vaccines:

3) What types of assays are available or need to be developed to demonstrate correlates of protection?

- Assays to measure antigen/antibody binding response (includes competitive inhibition ELISAs)
- Also need to establish relevant functional assays
  Possible examples:
  macrophage cytotoxicity assays (specific for V),
  assays specific for F1?

To Establish Correlates of Protection

1. Active Immunization Studies

Evaluate immune response in appropriate animal models (animal correlate of protection)

Evaluate immunogenicity in humans (clinical trials)

Compare the quality of the immune responses between animals and humans

Estimate the magnitude of the immune response that would protect humans (human correlate of protection)

Evaluation of efficacy in appropriate animal models

2. Passive Immunization Studies

- in the past, passive protection studies used to evaluate the killed whole cell plague vaccine and recent data indicate that passive immunization with anti-F1+V sera can confer protection

- passively immunize animals with human antibodies (clinical trials) and determine the level of antibody that protects animals from challenge

- from these studies can estimate the magnitude of the human antibody response that would provide protection in humans

Evaluation of efficacy in appropriate animal models

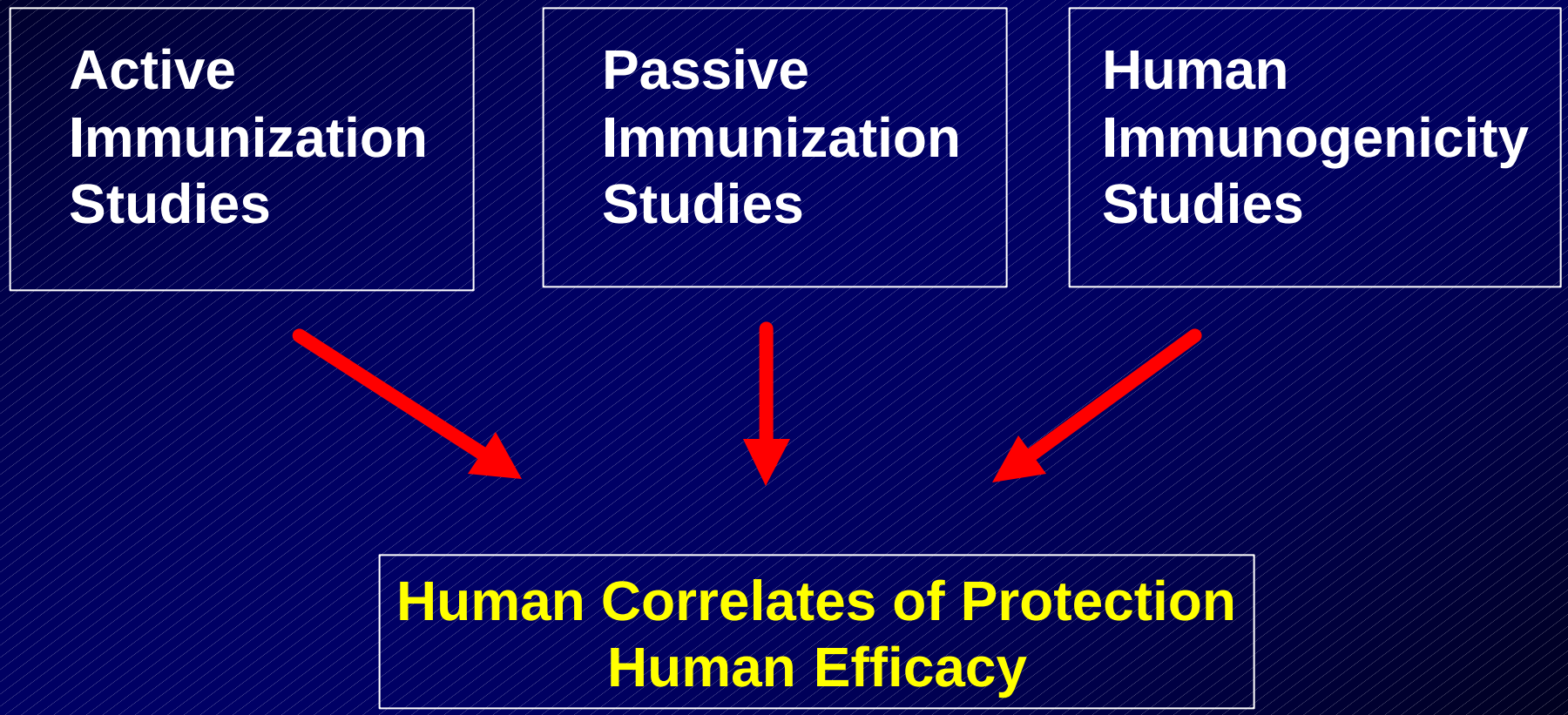
3. Time Course of the Immune and Memory Response

Active immunization studies in appropriate animal models

Human immunogenicity data from clinical trials

- Are similar immune responses elicited?
- Is the time course of the immune response similar after boost?
- Is the rate of antibody decline similar?

To Establish Correlates of Protection



Acknowledgements

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This presentation outlines strategies that may be used in the development of correlates of protection and is simply meant to be a starting point for discussions..